Natural resolution of peanut allergy: A 12-year longitudinal follow-up study

Philippe Bégin, MD, MS, FRCPC[a,b],
Louis Paradis, MD, FRCPC, FAAAAI[a,b],
Jean Paradis, MD, FRCPC[a,b],
Matthieu Picard, MD, FRCPC[a], and
Anne Des Roches, MD, FRCPC, FAAAAI[a]

Clinical Implication

- Spontaneous resolution of early-onset peanut allergy occurs predominantly before 6 years of age and at a much lower frequency after 10 years of age.

TO THE EDITOR:

Although retrospective case-control studies have shown that some children will naturally resolve their peanut allergy, the question remains as to how long they should wait for it to happen and how the probability varies over time.[1-3] Only one prospective study from Australia described the longitudinal evolution of the disease from diagnosis with an overall resolution rate of 18.4%.[4] However, it remains unclear whether more patients could have achieved tolerance were they given more time, because mean follow-up was limited to 5 years.

To further investigate this issue and to describe the natural evolution of the disease into early adolescence, we conducted a prospective longitudinal study of 202 children with early-onset peanut allergy from early childhood (median age, 12.1 months) to adolescence (median age, 13 years).[5] For design of the study with description of the cohort, definitions, techniques, and statistical analysis, please see the Methods section in this article's Online Repository at www.jaci-inpractice.org.

Briefly, subjects were infants aged 18 months or younger consecutively recruited at our center between 1998 and 2001. Peanut allergy was defined as an IgE-mediated compatible reaction on ingestion of peanut within 6 months of recruitment *and* positive peanut skin prick test (SPT). Patients were followed with SPT and peanut-specific IgE (PN-IgE; Immulite; Siemens, Munich, Germany) at 1- to 2-year intervals. Double-blind, placebo-controlled peanut challenges were offered, starting at the age of 5 years, in patients with PN-IgE <15 kU/L.

Fourteen patients were lost during follow-up and were censored from survival analysis at that time. Seventy-nine subjects were offered double-blind, placebo controlled food challenge (DBPCFC), which 12 declined (Table I). Of the remaining subjects, 48 passed and 19 failed a first DBPCFC. Among the latter, 4 were later offered a second challenge and 3 passed, bringing the total of tolerant subjects to 51 of 202 (25.1%) at the end of the study. Initial characteristics of resolvers and persisters are described (see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org). The 109 patients who were not offered DBPCFC were regarded as having persistent peanut allergy on the basis of PN-IgE >15 kU/L (Immulite; Siemens).

TABLE I. Allergy tests at time of double-blind, placebo-controlled food challenge

	DBPCFC offered (n = 79)			
	Passed (n = 51)*	Failed (n = 20)†	Declined (n = 12)	DBPCFC not offered (n = 109)‡
Peanut-specific IgE				
<0.35 kU/L	38	8	1	0
0.35-0.69 kU/L	3	2	1	0
0.7-3.49 kU/L	10	10	1	0
3.5-14.9 kU/L	0	0	9	0
15-49.9 kU/L	0	0	0	13
50-100 kU/L	0	0	0	26
>100 kU/L	0	0	0	70
Peanut SPT				
<3 mm	22	2	0	0
3-7 mm	13	3	0	6
8-12 mm	12	10	8	40
13-19 mm	4	3	2	48
>20 mm	0	2	2	15

*Includes 3 subjects who previously failed challenge.
†Includes 2 failed challenges from a single patient.
‡Allergy tests at end of study in patients that were not offered DBPCFC.

Kaplan-Meier curve that describes peanut allergy resolution over time is presented in Figure 1. Most resolutions (80%) occurred before the age of 8 years with mean annual rates of 6.6, 2.2, and 0.6 per 100 patients per year for the ages between 3 and 6, 6 and 10, and 10 and 15 years, respectively. At time of diagnosis, the cumulative probability of having remitted peanut allergy by ages 4, 6, 8, 10, and 12 was of 10%, 18%, 22%, 26%, and 27%, respectively.

These results may appear to contrast with the previous longitudinal study from Australia which reported a cumulative risk of resolution of 22% at 5 years and 34.2% at 7 years.[4] However, these rates were probably overestimated because of accumulating losses to follow-up at the end of their study (mean follow-up of 5 years, age 6 years). A more accurate approach could be to compare the overall remission rate in their cohort (18.4%) with our cumulative remission rate at age 6 years (17.9%; 95% CI, 12.5%-23.5%), which would suggest the 2 studies are in fact concordant. The cumulative remission of 22% (95% CI, 15%-26%) at 8 years is also in line with previous retrospective case−control studies performed at that age.[1-3]

One limit to consider is that patients with PN-IgE >15 kU/L were not offered DBPCFC. Although Immulite (Siemens) is a valid system to determine specific IgE, its working parameters, including 95% positive predictive value, have not been reported for peanut allergy; thus, we cannot be sure that all these patients would have reacted to peanut if challenged. The cutoff for PN-IgE of 15 kU/L was chosen arbitrarily as a point at which patients would reasonably not be offered challenge in clinic. The consequence is that some of these presumed persisters may in fact have had resolved their allergy, possibly leading to an underestimation of resolution rates.

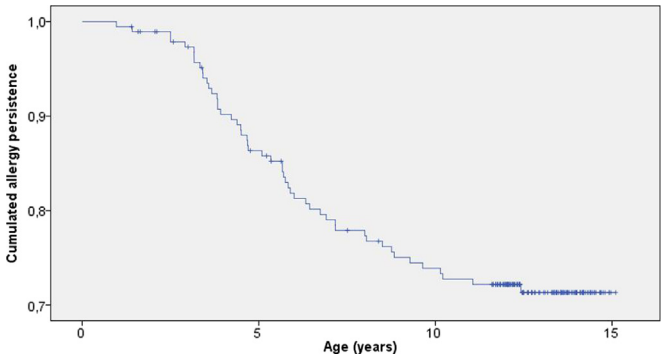

FIGURE 1. Cumulative probability of persistent peanut allergy diagnosis with time. *Vertical lines* indicate censored data (lost to follow-up). DBPCFCs were offered, starting at the age of 5 years. In patients who resolved their test before that age, time of allergy resolution was defined as time they resolved SPT and PN-IgE rather than as time of DBPCFC itself. The y-axis is truncated at its base, starting at 0.70.

Initial PN-IgE levels were generally low at time of diagnosis, which is expected in a population this young (median age, 12.1 months) (Table E2).[6] However, 39 subjects had PN-IgE <0.35 kU/L (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). These patients all reported an IgE-mediated compatible reaction to peanut and had SPT >4 mm which has been shown to carry a positive predictive value close to 100% before 2 years of age in previous studies.[7,8] Nevertheless, in the absence of DBPCFC at diagnosis, it cannot be excluded that some of these patients could have been tolerant to peanut to start with. As a group, they had a much more favorable evolution (overall resolution of 69%), and their inclusion in the study may have led to an overestimation of resolution rates. When considering only those patients with positive peanut serology at time of diagnosis, the overall probability of resolution dropped to 15%.

As a general rule, PN-IgE level increased progressively in persisters, whereas it remained low in remitters (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Initial PN-IgE >0.7 kU/L was the best predictor of persistence in multivariate analysis (hazard ratio, 3.44; $P < .0005$) (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). This being said, close to one-third of those with initial PN-IgE <0.35 kU/L still evolved into persistent disease (Table E3), and 1 of 4 patients with initial PN-IgE >17.5 kU/L eventually resolved. Evolution of SPT in the first years was also found useful to predict resolution. Peanut-specific SPT tended to decrease between the first and fourth years of life in resolvers (mean, -3.9 ± 6.6 mm), whereas it tended to increase in nonresolvers (mean, 1.7 ± 7.6 mm; $P < .0001$). These findings are in line with previous reports.[3,4]

Lack of trace avoidance was the only other variable associated with persistence in multivariate analysis (hazard ratio, 2.38; $P = .007$) (Table E4). This finding must be interpreted with caution because it is subject to recall bias and patient's perception of how well he or she complied with instructions for trace avoidance. It is however in accordance with previous literature showing that remitters who had introduced traces but not whole peanut in their diet were at higher risk of resensitization.[2,3,9] Although associated in univariate analysis, the severity and nature of the initial reaction as well as coexistent sensitizations failed to reach significance when controlled for initial PN-IgE levels (Tables E1 and E4).

In conclusion, spontaneous resolution of early-onset peanut allergy occurs predominantly before the age of 6 years and at a much lower frequency after the age of 10 years. Further follow-up will be needed to determine whether spontaneous resolution may still occur in this population in late adolescence or early adulthood.

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[a]Department of Pediatrics, Allergy and Clinical Immunology Division, Centre Hospitalier Universitaire Sainte-Justine, Montreal, Quebec, Canada
[b]Department of Medicine, Allergy and Clinical Immunology Unit, Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada

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Corresponding author: Anne Des Roches, MD, FRCPC, FAAAAI, Centre Hospitalier Universitaire Sainte-Justine, Allergy and Clinical Immunology Unit, 3175, Côte Sainte-Catherine, Montreal H3T 1C5, Canada. E-mail: a.des.roches@umontreal.ca.
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METHODS

Cohort

This cohort was described in a previous publication.[E1] Subjects were infants aged 18 months or younger diagnosed with peanut allergy and consecutively recruited between October 1998 and December 2001 at the Sainte-Justine University Hospital Center (Montreal, Quebec, Canada).

Definitions

Sensitization was defined as an SPT wheal size of 3 mm or larger.

Peanut allergy was defined as an unequivocal clinical reaction within the past 6 months *and* a SPT >3 mm compared with negative control.

A clinical reaction was defined as one or more symptoms in at least one of the following organ systems occurring immediately after contact with peanut (skin: hives, erythematous rash, angioedema; lower or upper respiratory tract: wheezing, repetitive cough, shortness of breath, rhinitis, conjunctivitis, voice change; gastrointestinal tract: vomiting, diarrhea; cardiovascular: altered consciousness). Additional food challenge was not performed on inclusion because of patients' age at enrollment.

Techniques

SPTs were performed for peanut and for a panel of inhalants and food allergens (Omega Laboratory, Montreal, Quebec, Canada) with the use of a number 25 sterile needle, as previously described.[E2-E4] Positive and negative controls were done with histamine 2 mg/mL and saline 0.9%, respectively. Serum total and specific IgE antibodies to peanut were measured with the Immulite immunoassay system (Siemens, Munich, Germany).

The DBPCFC protocol used an applesauce and oat mixture with either peanuts or soy nut to obtain a placebo with similar consistency. DBPCFC was performed over 2 separate days for each mixture in a random order. Parents, patient, and medical team were all blinded to the content of the mixture. Patient had to wear a nose plug and others had to wear a perfume-vaporized mask throughout the procedure. Challenge consists of 5 steps 20 minutes apart under medical supervision, with the administration of 0.1, 0.5, 2, 7, and 20 g of whole peanuts (in the nonplacebo mixture). These doses correspond to 30, 150, 600, 2000, and 5500 mg of peanut proteins, respectively. If no reaction had occurred 45 minutes after the second challenge, an open challenge with a peanut-containing candy bar was performed. A positive challenge result was recorded if an unequivocal objective reaction to peanut (ie, urticaria, erythematous rash; vomiting, diarrhea; sneezing, rhinorrhea, stridor, wheeze, cough; or anaphylaxis) was observed within 60 minutes of the intake of the last dose of peanut.

Design of the study

At enrollment, familial and personal coexistent atopic manifestations were documented. Parents were educated about stringent avoidance of dietary peanut and nuts, including avoiding products labeled "may contain traces of peanut" *and* banning peanuts and nuts from the child's home. All children underwent SPTs for peanut, cow's milk, hen's egg, soy, mixed nuts, sesame, wheat, and inhalants (*Dermatophagoides pteronyssinus* and *farinae*, dog and cat dander, molds, birch, ragweed, grass, and *Artemisia* pollens). Blood samples were collected for peanut-specific and total IgE dosages. Patients were followed at 1- to 2-year intervals. Peanut SPT and PN-IgE were repeated during the follow-up. Double-blind placebo-controlled peanut challenges were offered, starting at the age of 5 years in patients with PN-IgE <15 kU/L.

Statistical analysis

Categorical data of remitters and nonremitters were compared by using Fisher exact test. Continuous variables were compared by using the Student *t* test. By using the Youden index, the best cutoff point of initial SPT wheal diameter and peanut- and component-specific IgE levels for predicting tolerance was determined. Kaplan–Meier analysis was used to determine cumulative probability of resolution, and Cox regression modeling was used to calculate hazard ratios for covariate variables. Patients lost during follow-up were included in survival analyses and censored at the point when they were lost. Statistical analysis was performed with SPSS software version 17.0.1 (SPSS Inc, Chicago, Ill).

Approval for this study was granted by our institutional Ethical Review Board.

TABLE E1. Clinical features of remitters and nonremitters with early-onset peanut allergy

	Remitters (n = 51)	Nonremitters (n = 151)	RR	95% CI	Unajusted *P* value
Male, no (%)	27 (53)	92 (61)	1.09	0.92-1.31	.33
Age at enrollment (mo), mean ± SD	14.8 ± 2.4	13.2 ± 1.0	—	—	—
Age at end of follow-up (y)					
Mean ± SD	13.5 ± 1.1	12.5 ± 2.9			
Median	13.3	13.2			
Father atopy, no. (%)	21 (41)	81 (54)	1.13	0.96-1.34	.15
Mother atopy, no. (%)	25 (49)	90 (60)	1.12	0.94-1.33	.19
Index reaction, no. (%)					
Cutaneous	50 (98)	148 (98)	1.00	0.75-3.41	>.99
Urticaria	48 (94)	119 (79)	0.78	0.72-0.96	.01*
Angioedema	25 (49)	83 (55)	1.06	0.90-1.26	.52
Respiratory	5 (10)	31 (21)	1.19	0.94-1.34	.09
Gastrointestinal	1 (2)	29 (19)	1.36	1.12-1.42	.001*
Altered consciousness	1 (2)	8 (5)	1.20	0.68-1.35	.32
Anaphylaxis (2 systems)	7 (14)	43 (28)	1.21	1.00-1.36	.04*
Coexistent atopic diagnoses at initial visit, no. (%)					
Atopic dermatitis	38 (75)	115 (76)	1.02	0.86-1.29	.85
Asthma	5 (10)	26 (17)	1.15	0.88-1.32	.26
Bronchiolitis	14 (27)	29 (19)	0.88	0.67-1.08	.24
Rhinitis	12 (24)	44 (29)	1.07	0.87-1.25	.48
Other food allergy	20 (39)	59 (39)	1.00	0.83-1.18	>.99
Coexistent atopic diagnoses at final follow-up, no. (%)					
Atopic dermatitis	20 (39)	53 (35)	0.96	0.79-1.13	.62
Asthma	16 (31)	100 (66)	1.45	1.21-1.72	<.0005*
Rhinitis	25 (49)	121 (80)	1.55	1.22-2.02	<.0005*
Other food allergy	14 (27)	90 (60)	1.39	1.17-1.61	<.0005*
Environmental factors, no. (%)					
Breast-feeding	40 (78)	130 (86)	1.17	0.92-1.63	.27
Strict avoidance of traces	36 (71)	79 (52)	0.83	0.72-0.98	.02*
Other sensitizations at initial visit, no. (%)					
Sesame	12 (24)	22 (15)	0.84	0.61-1.07	.19
Egg	30 (59)	93 (62)	1.03	0.87-1.24	.74
Milk	2 (4)	10 (7)	1.12	0.68-1.32	.73
Nuts	6 (12)	46 (30)	1.26	1.05-1.40	.009*
Soy	2 (4)	3 (2)	0.79	0.23-1.25	.60
Wheat	0	7 (5)	1.35	0.76-1.35	.20
Inhalant allergens	14 (27)	75 (50)	1.25	1.05-1.44	.006*
Total IgE ≥100 kU/L at initial visit, no. (%)	4 (8)	36 (24)	1.27	1.04-1.40	.01*
Mean Δ peanut SPT (1-4 y) (mm), mean ± SD	−3.9 ± 6.6	1.2 ± 7.7	—	—	<.0001*

*Statistically significant.

TABLE E2. Initial SPT and IgE characteristics of remitters and nonremitters with early-onset peanut allergy

	Remitters, no. (%) (n = 51)	Nonremitters, no. (%) (n = 151)	*Z* score	Unajusted *P* value
Peanut SPT at initial visit			3.42	.0006*
3-7 mm	29 (57)	39 (26)		
8-12 mm	13 (25)	60 (40)		
13-19 mm	4 (8)	44 (29)		
≥20 mm	5 (10)	8 (5)		
Peanut-specific IgE at initial visit			5.89	<.00005*
<0.35 kU/L	27 (53)	12 (8)		
0.35-0.69 kU/L	6 (21)	14 (9)		
0.70-3.49 kU/L	13 (25)	93 (62)		
3.50-17.49 kU/L	4 (8)	29 (10)		
≥17.5 kU/L	1 (2)	3 (1)		

*Statistically significant.

TABLE E3. Very low initial PN-IgE (<0.35 KU/L) subgroup

	Remitters, no. (n = 27)	Nonremitters, no. (n = 12)	*Z* score	Unajusted *P* value
Peanut SPT at initial visit			1.40	.16
4-7 mm	18	5		
8-12 mm	5	4		
13-19 mm	4	3		
≥20 mm	0	0		
Peak peanut-specific IgE during follow-up			4.57	<.00005*
<0.10 kU/L	9	2		
0.10-0.34 kU/L	13	0		
0.35-0.69 kU/L	1	0		
0.70-3.49 kU/L	3	1		
3.50-17.4 kU/L	1	3		
17.5- 49.9 kU/L	0	1		
50-100 kU/L	0	3		
>100 kU/L	0	2		
Total IgE >100 kU/L at initial visit	0	0		

*Statistically significant.

TABLE E4. Predictors for early-onset peanut allergy persistence according to multivariate analysis

	HR	95% CI	Adjusted *P* value
Initial PN-IgE ≥0.70 kU/L	3.44	1.74-6.80	<.0005*
Lack of stringent control of traces	2.42	1.28-4.58	.007*
Initial peanut SPT ≥8 mm	1.76	0.96-3.22	.07
Initial reaction involving GI tract	6.69	0.76-59.26	.09
Sensitization to nuts	1.91	0.66-5.52	.23
Total IgE ≥100 kU/L	1.43	0.56-3.68	.46
Inhalant allergen sensitization	1.30	0.63-2.68	.48
Lack of urticaria on initial reaction	1.56	0.44-5.46	.49
Anaphylaxis on initial reaction	1.21	0.46-3.14	.70

GI, Gastrointestinal; *HR*, hazard ratio.
*Statistically significant.

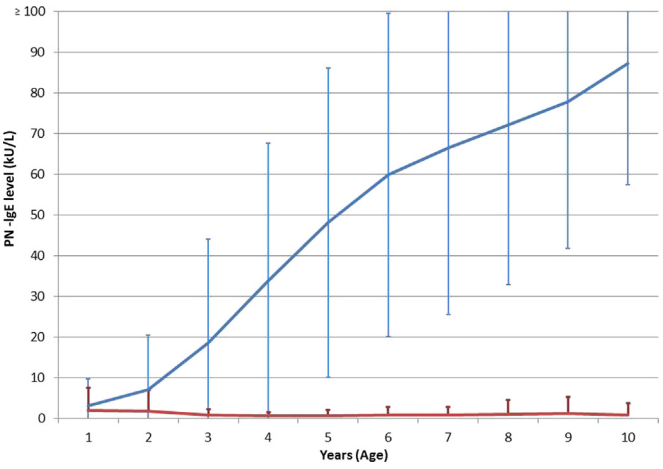

FIGURE E1. Evolution peanut-specific IgE in remitters and nonremitters. *Blue* and *red lines* correspond to PN-IgE mean within the persisters and remitters group, respectively. *Vertical error lines* indicate SD.

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